REMARKS:

In the Office Action dated October 21, 2008, claims 40-45, 47 and 48, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 40-45 and 47-48 remain in this application, claims 1-39, and 46 have been canceled and new claim 49 has been added to the application. New claim 49 was previously indicated as allowable during a conversation with the Examiner in 2002.

Claims 40-45, 47 and 48 were rejected under 35 USC §112, first paragraph, as lacking an adequate written description regarding "G protein mediated extracellular signal transduction pathway". The claims have been amended to indicate that the growth factor receptor is mediated by its extracellular domain in a G protein mediated signal transduction. Page 3 of the office action indicates that such language is supported by the present application. Regarding the language " a compound which acts on a growth factor receptor" and "a compound which directly acts on a growth factor precursor", this language is supported by the disclosure on page 2, third paragraph and page 3, line 15. This disclosure indicates that the modulator according to the present invention acts on a growth factor precursor and shows a specific compound which directly binds to a growth factor precursor. The above amendments are believed to overcome the rejections of the claims regarding the types of cancer cells. In view of the above amendments, applicants request that this rejection be withdrawn.

Claims 40-45, 47 and 48 were rejected under 35 USC § 112, first paragraph as lacking enablement. Applicants point out that this rejection was previously made in the office action dated May 21, 2002 but was not repeated in the May 20, 2003 office action and thus was apparently overcome. Applicants respectfully contend that the present invention is useful for receptor tyrosine kinases other than the EGF receptor. The previously submitted references (discussed in applicant's February 21, 2003 supplemental response), Kotecha et al., Waters, et al., Bogulawski et al., Oak et al., Saito and Berk, Rueda et al., Heeneman et al., Miura et al., Tanimoto et al., Lee et al., Belcheva et al., Peng et al., and Sumitomo et al., demonstrate that G protein or GPCR mediated transactivation not only takes place with EGFR, but also with other receptor tyrosine kinases such as PDGFR, KDR/FLK-1, TRK receptor, fibroblast growth factor receptor 1 and IGFR-1. All of these references were published in 2001 and 2002 and reflect the impact of the scientific achievement of the present invention, wherein the connection between G protein/GPCR mediated signal transduction and transactivation of receptor tyrosine kinases has been elucidated for the first time.

Applicants also contend that the present invention works with inhibitors other than inhibitors of metalloproteinase dependent cleavage. Schraufstatter et al., Oak et al., Filardo et al., Kalmes et al., McCole et al., Yan et al., and Pai et al. (abstracts submitted with the 2003 response) clearly demonstrate that other types of inhibitors are capable of blocking receptor tyrosine kinase transactivation. Experimental data was also attached to applicant's 2003 supplemental response which shows that anti-HB-EGF antibodies are capable of blocking receptor tyrosine kinase transactivation.

In view of the above amendments and discussion, applicants request that this rejection be withdrawn.

Claims 40-45, 47 and 48 were rejected under 35 USC §112, second paragraph, as indefinite. The claims have been amended to indicate that the growth factor receptor tyrosine kinase activation is modulated by interrupting G-protein mediated signal transduction. In addition, claim 45 has been amended to indicate that one or more tyrosine residues of the growth factor receptor are phosphorylated. In view of these amendments, applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of claims 40-45 and 47-49 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

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